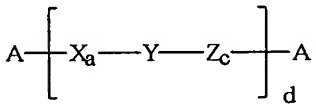
CLAIMS

What is claimed is:

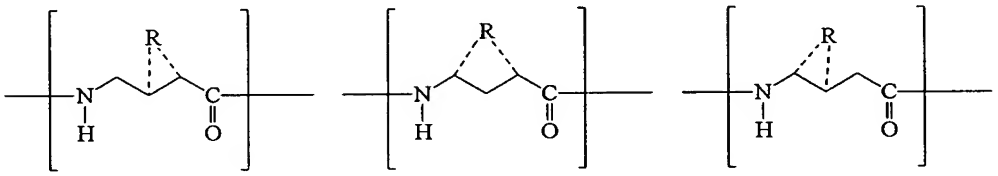
1. An isolated, unnatural polypeptide compound selected from the group consisting of:



wherein:

each X and each Z is independently variable and is selected from the group consisting of α-amino acid residues, β-amino acid residues, and γ-amino acid residues, provided that at least one X or Z comprises an α-amino acid residue and at least another two of X or Z comprise two cyclically-constrained γ-amino acid residues; and

wherein each cyclically-constrained γ-amino acid residue is independently selected from the group consisting of:



wherein R, together with the carbons to which it is attached, and further together with the β-position carbon in the γ-amino acid backbone where appropriate, independently defines a substituted or unsubstituted, monocyclic or bicyclic C_4 to C_{10} cycloalkyl, cycloalkenyl, or heterocycle moiety, the heterocycle moiety having 1, 2, or 3 heteroatoms selected from the group consisting of N, S, and O; and

each "Y" is independently variable and is a single bond or a reverse-turn moiety; and

each "A" is independently selected from the group consisting of hydrogen, hydroxy, an amino-terminus protecting group, and a carboxy-terminus protecting group; and

each "a," "c," and "d" is an independently variable positive integer, and wherein "a" + "c" > 3; and

salts thereof.

2. The compound of Claim 1, wherein each R, together with the carbons to which it is attached and together with a β-position carbon in the γ-amino acid backbone when the β-position carbon is present, independently defines a substituted C_5 to C_6 cycloalkyl, cycloalkenyl, or heterocycle moiety having a single nitrogen heteroatom; and

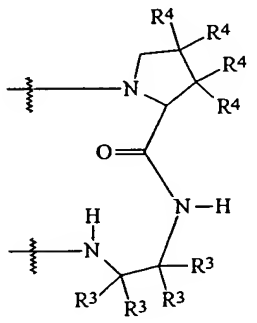
substituents on the cycloalkyl, cycloalkenyl, or heterocycle moieties are independently selected from the group consisting of linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, $-(CH_2)_{n+1}-OR^2$, $-(CH_2)_{n+1}-SR^2$, $-(CH_2)_{n+1}-S(=O)-CH_2-R^2$, $-(CH_2)_{n+1}-S(=O)_2-CH_2-R^2$, $-(CH_2)_{n+1}-NR^2R^2$, $-(CH_2)_{n+1}-NHC(=O)R^2$, $-(CH_2)_{n+1}-NHS(=O)_2-CH_2-R^2$, $-(CH_2)_{n+1}-O-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-S-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-S(=O)-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-S(=O)_2-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-NH-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-N-\{(CH_2)_m-R^1\}_2$, $-(CH_2)_{n+1}-NHC(=O)-(CH_2)_{n+1}-R^1$, $-(CH_2)_{n+1}-NHS(=O)_2-(CH_2)_m-R^1$; $-(CH_2)_n-OR$, $-(CH_2)_n-SR^2$, $-(CH_2)_n-S(=O)-CH_2-R^2$, $-(CH_2)_n-S(=O)_2-CH_2-R^2$, $-(CH_2)_n-NR^2R^2$, $-(CH_2)_n-NHC(=O)R^2$, $-(CH_2)_n-NHS(=O)_2-CH_2-R^2$, $-(CH_2)_n-O-(CH_2)_m-R^1$, $-(CH_2)_n-S-(CH_2)_m-R^1$, $-(CH_2)_n-S(=O)-(CH_2)_m-R^1$, $-(CH_2)_n-S(=O)_2-(CH_2)_m-R^1$, $-(CH_2)_n-NH-(CH_2)_m-R^1$, $-(CH_2)_n-N-\{(CH_2)_m-R^1\}_2$ $-(CH_2)_n-NHC(=O)-(CH_2)_m-R^1$, and $-(CH_2)_n-NHS(=O)_2-(CH_2)_m-R^1$;

wherein m is an integer of from 2-6 and n is an integer of from 0-6;

wherein R^2 is independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

wherein R^1 is selected from the group consisting of hydroxy, C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, C_1-C_6-alkyl ester, aryl ester, heteroaryl ester, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane.

3. The compound of Claim 1, wherein each Y is a single bond or a reverse turn moiety independently selected from group consisting of a prolyl-glycolic acid residue, a di-nipecotic acid residue, or a compound of the following formula:

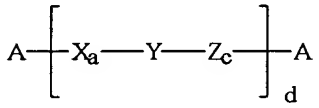


where each R^3 is independently variable and is selected from the group consisting of hydrogen, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, and mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

where each R^4 is selected from the group consisting of hydroxy, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl; mono- or bicyclic heteroaryl-C_1-C_6-alkyl; C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-

arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane.

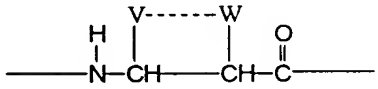
4. An isolated, unnatural polypeptide compound selected from the group consisting of:



wherein:

each X and each Z is independently variable and is selected from the group consisting of α-amino acid residues, β-amino acid residues, and γ-amino acid residues, provided that at least one X or Z comprises an α-amino acid residue and at least another two of X or Z comprise two cyclically-constrained β-amino acid residues; and

wherein each cyclically-constrained β-amino acid residue is independently selected from the group consisting of:



wherein V and W are combined, together with the carbon atoms to which they are bonded, and independently define a substituted or unsubsituted,

monocyclic or bicyclic C_3-C_{10} cycloalkyl, cycloalkenyl or heterocyclic ring having one or more N, O or S atom(s) as the heteroatom(s);

the substituents on carbon atoms of the rings being independently selected from the group consisting of linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, and the substituents listed above for V and W when V and W are not combined;

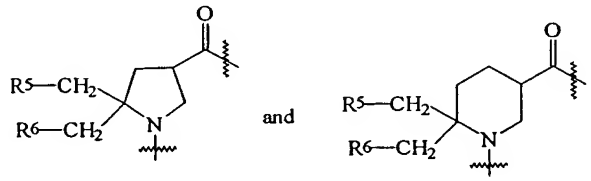
the substituents on nitrogen heteroatoms of the rings being independently selected from the group consisting of hydrogen, monocyclic or bicyclic C_1-C_{10}-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, $-S(=O)_2-R^{17}$, $-C(=O)-R^{17}$, $-S(=O)_2-(CH_2)_{n+1}-R^{18}$, and $-C(=O)-(CH_2)_n-R^{18}$, where n = 1 to 6;

wherein R^{17} is independently selected from the group consisting of hydrogen, monocyclic or bicyclic C_1-C_{10}-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

wherein R^{18} is independently selected from the group consisting of hydroxy, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl; mono- or bicyclic heteroaryl-C_1-C_6-alkyl; C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl,

heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and

wherein each cyclically-constrained β-amino acid residue is further selected from the group consisting of:



wherein R^5 and R^6 are independently selected from the group consisting of hydrogen, hydroxy, linear, branched, or cyclic C_1-C_{16}-alkyl, alkenyl, or alkynyl; mono-or di- C_1–C_{16} alkylamino; mono- or bicyclic aryl; mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_{16}-alkyl; mono- or bicyclic heteroaryl-C_1-C_{16}-alkyl; $-(CH_2)_{0-6}-OR^7$, $-(CH_2)_{0-6}-SR^7$, $-(CH_2)_{0-6}-S(=O)-$

CH_2-R^7, -$(CH_2)_{0-6}$-S(=O)$_2$-CH_2-R^7, -$(CH_2)_{0-6}$-NR^7R^7, -$(CH_2)_{0-6}$-NHC(=O)R^7, -$(CH_2)_{0-6}$-NHS(=O)$_2$-CH_2-R^7, -$(CH_2)_{0-6}$-C(=O)-OH, -$(CH_2)_{0-6}$-C(=O)-OR^7, -$(CH_2)_{0-6}$-C(=O)-NH_2, -$(CH_2)_{0-6}$-C(=O)-NHR^7, -$(CH_2)_{0-6}$-C(=O)-N(R^7)$_2$, -$(CH_2)_{0-6}$-O-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-S-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-S(=O)-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-S(=O)$_2$-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-NH-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-N-{$(CH_2)_{2-6}$-R^8}$_2$, -$(CH_2)_{0-6}$-NHC(=O)-$(CH_2)_{2-6}$-R^8, and -$(CH_2)_{0-6}$-NHS(=O)$_2$-$(CH_2)_{2-6}$-R^8;

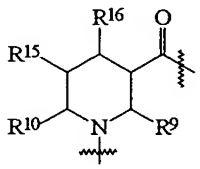
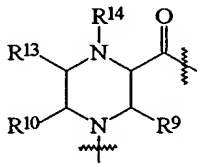
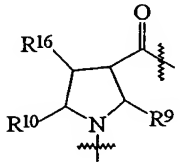
wherein

R^7 is independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

R^8 is selected from the group consisting of hydroxy, C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl,

heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and

wherein each cyclically-constrained β-amino acid residues is further selected from the group consisting of:



and


wherein R^9, R^{10}, and R^{13} are independently selected from the group consisting of hydrogen, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono-or di- C_1–C_6 alkylamino, mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, $-(CH_2)_{1-6}-OR^{11}$, $-(CH_2)_{1-6}-SR^{11}$, $-(CH_2)_{1-6}-S(=O)-CH_2-R^{11}$, $-(CH_2)_{1-6}-S(=O)_2-CH_2-R^{11}$, $-(CH_2)_{1-6}-NR^{11}R^{11}$, $-(CH_2)_{1-6}-NHC(=O)R^{11}$, $-(CH_2)_{1-6}-NHS(=O)_2-CH_2-R^{11}$, $-(CH_2)_{0-6}-C(=O)-OH$, $-(CH_2)_{0-6}-C(=O)-OR^{11}$, $-(CH_2)_{0-6}-C(=O)-NH_2$, $-(CH_2)_{0-6}-C(=O)-NHR^{11}$, $-(CH_2)_{0-6}-C(=O)-N(R^{11})_2$, $-(CH_2)_{1-6}-O-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-S-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-S(=O)-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-S(=O)_2-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-NH-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-N-\{(CH_2)_{2-6}-R^{12}\}_2$, $-(CH_2)_{1-6}-NHC(=O)-(CH_2)_{2-6}-R^{12}$, and $-(CH_2)_{1-6}-NHS(=O)_2-(CH_2)_{2-6}-R^{12}$; wherein

R^{11} is independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

R^{12} is selected from the group consisting of hydroxy, C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane;

R^{14} is selected from the group consisting of hydrogen, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono-or di- C_1–C_6 alkylamino, mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, $-S(=O)_2-(CH_2)_{1-6}-R^{11}$, $-C(=O)R^{11}$, $-S(=O)_2-(CH_2)_{2-6}R^{12}$, and $-C(=O)-(CH_2)_{1-6}-R^{12}$; wherein R^{11} and R^{12} are as defined above;

R^{15} and R^{16} are selected from the group listed above for R^9, R^{10},and R^{13}, and are further selected from the group consisting of hydroxy, C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl,

arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and

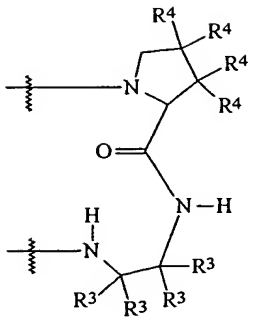
each "Y" is independently variable and is a single bond or a reverse-turn moiety; and

each "A" is independently selected from the group consisting of hydrogen, hydroxy, an amino-terminus protecting group, and a carboxy-terminus protecting group; and

each "a," "c," and "d" is an independently variable positive integer, and wherein "a" + "c" > 3; and

salts thereof.

5. The compound of Claim 4, wherein each Y is a single bond or a reverse turn moiety independently selected from group consisting of a prolyl-glycolic acid residue, a di-nipecotic acid residue, or a compound of the following formula:

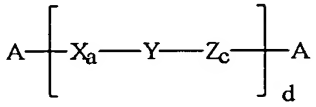


where each R^3 is independently variable and is selected from the group consisting of hydrogen, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, and mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

where each R^4 is selected from the group consisting of hydroxy, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl; mono- or bicyclic heteroaryl-C_1-C_6-alkyl; C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-

substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane.

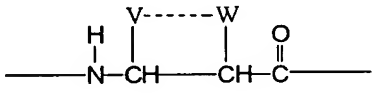
6. An isolated, unnatural polypeptide compound selected from the group consisting of:



wherein:

each X and each Z is independently variable and is selected from the group consisting of α-amino acid residues, β-amino acid residues, and γ-amino acid residues, provided that at least one X or Z is an α-amino acid residue and at least another two of X or Z comprise two cyclically-constrained residues, the two cyclically-constrained residues comprising cyclically-constrained β-amino acid residues or cyclically-constrained γ-amino acid residues, or one cyclically-constrained β-amino acid residue and one cyclically-constrained γ-amino acid residue; and

wherein the cyclically-constrained β-amino acid residues are selected from the group consisting of:



wherein V and W are combined, together with the carbon atoms to which they are bonded, and independently define a substituted or unsubsituted, monocyclic or bicyclic C_3-C_{10} cycloalkyl, cycloalkenyl or heterocyclic ring having one or more N, O or S atom(s) as the heteroatom(s);

the substituents on carbon atoms of the rings being independently selected from the group consisting of linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, and the substituents listed above for V and W when V and W are not combined;

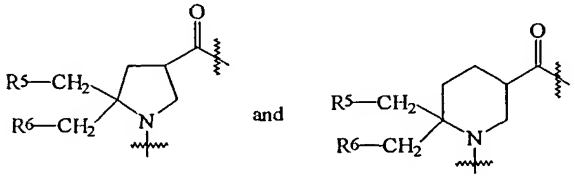
the substituents on nitrogen heteroatoms of the rings being independently selected from the group consisting of hydrogen, monocyclic or bicyclic C_1-C_{10}-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, $-S(=O)_2-R^{17}$, $-C(=O)-R^{17}$, $-S(=O)_2-(CH_2)_{n+1}-R^{18}$, and $-C(=O)-(CH_2)_n-R^{18}$, where n = 1 to 6;

wherein R^{17} is independently selected from the group consisting of hydrogen, monocyclic or bicyclic C_1-C_{10}-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

wherein R^{18} is independently selected from the group consisting of hydroxy, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl; mono- or bicyclic heteroaryl-C_1-C_6-alkyl; C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-

arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and

wherein the cyclically-constrained β-amino acid residues are further selected from the group consisting of:



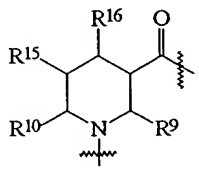
wherein R^5 and R^6 are independently selected from the group consisting of hydrogen, hydroxy, linear, branched, or cyclic C_1-C_{16}-alkyl, alkenyl, or alkynyl; mono-or di- C_1–C_{16} alkylamino; mono- or bicyclic aryl; mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_{16}-alkyl; mono- or bicyclic heteroaryl-C_1-C_{16}-alkyl; -$(CH_2)_{0-6}$-OR^7, -$(CH_2)_{0-6}$-SR^7, -$(CH_2)_{0-6}$-S(=O)-CH_2-R^7, -$(CH_2)_{0-6}$-$S(=O)_2$-CH_2-R^7, -$(CH_2)_{0-6}$-NR^7R^7, -$(CH_2)_{0-6}$-NHC(=O)R^7, -$(CH_2)_{0-6}$-NHS$(=O)_2$-CH_2-R^7, -$(CH_2)_{0-6}$-C(=O)-OH, -$(CH_2)_{0-6}$-C(=O)-OR^7, -$(CH_2)_{0-6}$-C(=O)-NH_2, -$(CH_2)_{0-6}$-

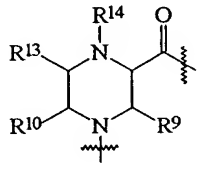
$C(=O)$-NHR^7, -$(CH_2)_{0-6}$-$C(=O)$-$N(R^7)_2$, -$(CH_2)_{0-6}$-O-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-S-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-$S(=O)$-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-$S(=O)_2$-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-NH-$(CH_2)_{2-6}$-R^8, -$(CH_2)_{0-6}$-N-$\{(CH_2)_{2-6}$-$R^8\}_2$, -$(CH_2)_{0-6}$-$NHC(=O)$-$(CH_2)_{2-6}$-R^8, and -$(CH_2)_{0-6}$-$NHS(=O)_2$-$(CH_2)_{2-6}$-R^8; wherein

R^7 is independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

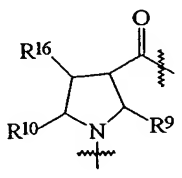
R^8 is selected from the group consisting of hydroxy, C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane;

and wherein the cyclically-constrained β-amino acid residues are further selected from the group consisting of:





and



wherein R^9, R^{10}, and R^{13} are independently selected from the group consisting of hydrogen, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono-or di- C_1–C_6 alkylamino, mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, $-(CH_2)_{1-6}-OR^{11}$, $-(CH_2)_{1-6}-SR^{11}$, $-(CH_2)_{1-6}-S(=O)-CH_2-R^{11}$, $-(CH_2)_{1-6}-S(=O)_2-CH_2-R^{11}$, $-(CH_2)_{1-6}-NR^{11}R^{11}$, $-(CH_2)_{1-6}-NHC(=O)R^{11}$, $-(CH_2)_{1-6}-NHS(=O)_2-CH_2-R^{11}$, $-(CH_2)_{0-6}-C(=O)-OH$, $-(CH_2)_{0-6}-C(=O)-OR^{11}$, $-(CH_2)_{0-6}-C(=O)-NH_2$, $-(CH_2)_{0-6}-C(=O)-NHR^{11}$, $-(CH_2)_{0-6}-C(=O)-N(R^{11})_2$, $-(CH_2)_{1-6}-O-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-S-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-S(=O)-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-S(=O)_2-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-NH-(CH_2)_{2-6}-R^{12}$, $-(CH_2)_{1-6}-N-\{(CH_2)_{2-6}-R^{12}\}_2$, $-(CH_2)_{1-6}-NHC(=O)-(CH_2)_{2-6}-R^{12}$, and $-(CH_2)_{1-6}-NHS(=O)_2-(CH_2)_{2-6}-R^{12}$; wherein

R^{11} is independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

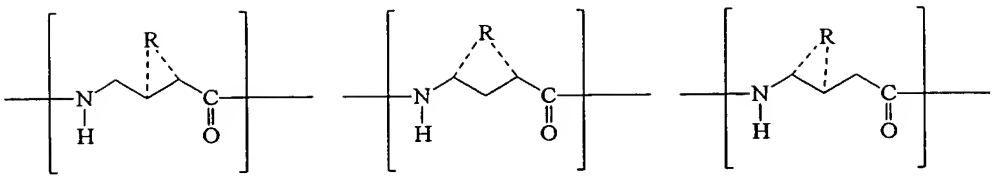
R^{12} is selected from the group consisting of hydroxy, C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-

heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane;

R^{14} is selected from the group consisting of hydrogen, linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono-or di- C_1–C_6 alkylamino, mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, $-S(=O)_2-(CH_2)_{1-6}-R^{11}$, $-C(=O)R^{11}$, $-S(=O)_2-(CH_2)_{2-6}R^{12}$, and $-C(=O)-(CH_2)_{1-6}-R^{12}$; wherein R^{11} and R^{12} are as defined above;

R^{15} and R^{16} are selected from the group listed above for R^9, R^{10},and R^{13}, and are further selected from the group consisting of hydroxy, C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and

wherein the cyclically-constrained γ-amino acid residues are selected from the group consisting of:



wherein R, together with the carbons to which it is attached, and further together with the β-position carbon in the γ-amino acid backbone where appropriate, independently defines a substituted or unsubstituted, monocyclic or bicyclic C_3 to C_{10} cycloalkyl, cycloalkenyl, or heterocycle moiety, the heterocycle moiety having 1, 2, or 3 heteroatoms selected from the group consisting of N, S, and O; and

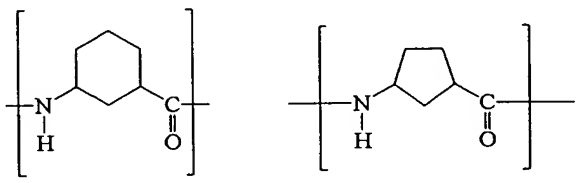
each "Y" is independently variable and is a single bond or a reverse-turn moiety; and

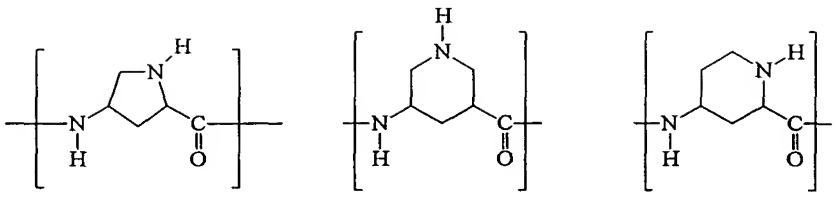
each "A" is independently selected from the group consisting of hydrogen, hydroxy, an amino-terminus protecting group, and a carboxy-terminus protecting group; and

each "a," "c," and "d" is an independently variable positive integer, and wherein "a" + "c" > 3; and

salts thereof.

7. The compound of Claim 6, wherein at least one of X or Z is a cyclically-constrained γ-amino acid residue independently selected from the group consisting of:





8. The compound of Claim 6, wherein at least one of X or Z is a cyclically-constrained β-amino acid residue wherein V and W, and the carbon atoms to which they are bonded, define a substituted or unsubstituted C_4 to C_6 cycloalkyl, cycloalkenyl, or heterocyclic ring having one nitrogen atom as the sole heteratom.

9. The compound of Claim 6, wherein at least one of X or Z is a cyclically-constrained β-amino acid residue wherein V and W, and the carbon atoms to which they are bonded, define a substituted or unsubstituted cyclopentyl, cyclohexyl, pyrrolidinyl, or piperdinyl ring.

10. The compound of Claim 6, wherein at least one of X or Z is a cyclically-constrained γ-amino acid residue wherein each R, together with the carbons to which it is attached and together with the β-position carbon in the γ-amino acid backbone where appropriate, independently defines a substituted C_5 to C_6 cycloalkyl, cycloalkenyl, or heterocycle moiety having a single nitrogen heteroatom; and

substituents on the cycloalkyl, cycloalkenyl, or heterocycle moieties are independently selected from the group consisting of linear, branched, or cyclic C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl, $-(CH_2)_{n+1}-OR^2$, $-(CH_2)_{n+1}-SR^2$, $-(CH_2)_{n+1}-S(=O)-CH_2-R^2$, $-(CH_2)_{n+1}-S(=O)_2-CH_2-R^2$, $-(CH_2)_{n+1}-NR^2R^2$, $-(CH_2)_{n+1}-$

$NHC(=O)R^2$,$-(CH_2)_{n+1}-NHS(=O)_2-CH_2-R^2$, $-(CH_2)_{n+1}-O-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-S-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-S(=O)-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-S(=O)_2-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-NH-(CH_2)_m-R^1$, $-(CH_2)_{n+1}-N-\{(CH_2)_m-R^1\}_2$, $-(CH_2)_{n+1}-NHC(=O)-(CH_2)_{n+1}-R^1$, $-(CH_2)_{n+1}-NHS(=O)_2-(CH_2)_m-R^1$; $-(CH_2)_n-OR$,$-(CH_2)_n-SR^2$, $-(CH_2)_n-S(=O)-CH_2-R^2$, $-(CH_2)_n-S(=O)_2-CH_2-R^2$, $-(CH_2)_n-NR^2R^2$, $-(CH_2)_n-NHC(=O)R^2$, $-(CH_2)_n-NHS(=O)_2-CH_2-R^2$, $-(CH_2)_n-O-(CH_2)_m-R^1$, $-(CH_2)_n-S-(CH_2)_m-R^1$, $-(CH_2)_n-S(=O)-(CH_2)_m-R^1$, $-(CH_2)_n-S(=O)_2-(CH_2)_m-R^1$, $-(CH_2)_n-NH-(CH_2)_m-R^1$, $-(CH_2)_n-N-\{(CH_2)_m-R^1\}_2$ $-(CH_2)_n-NHC(=O)-(CH_2)_m-R^1$, and $-(CH_2)_n-NHS(=O)_2-(CH_2)_m-R^1$;

wherein m is an integer of from 2-6 and n is an integer of from 0-6;

wherein R^2 is independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C_1-C_6-alkyl, mono- or bicyclic heteroaryl-C_1-C_6-alkyl; and

wherein R^1 is selected from the group consisting of hydroxy, C_1-C_6-alkyloxy, aryloxy, heteroaryloxy, thio, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C_1-C_6-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C_1-C_6-alkylamino, carboxylic acid, carboxamide, mono- or di-C_1-C_6-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C_1-C_6-alkylsulfonamide, mono- or diarylsulfonamide, mono- or

diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the subsitutent(s) is selected from the group consisting of C_1-C_6-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane.

11. A method of probing, disrupting, or mimicking binding interactions between two protein molecules or fragments thereof, the method comprising:

in an *in vivo*, *in vitro*, or *ex vivo* reaction between the two proteins,

(a) introducing to the reaction an unnatural polypeptide compound according to Claim 1; and then

(b) quantifying any effect of the added compound from step (a) on thermodynamic or kinetic parameters of the binding interaction between the two protein molecules or fragments thereof.

12. An isolated, unnatural polypeptide comprising four or more residues, wherein each residue is independently selected from the group consisting of α-amino acid residues, cyclically-constrained β-amino acid residues, and cyclically-constrained γ-amino acid residues, and further wherein at least two of the residues are cyclically-constrained β-amino acid residues or cyclically-constrained γ-amino acid residues or one each of a cyclically-constrained β-amino acid residue and a cyclically-constrained γ-amino acid residue.

13. An isolated, unnatural polypeptide comprising four or more residues, wherein each residue is independently selected from the group consisting of cyclically-constrained β-amino acid residues and cyclically-constrained γ-amino acid residues, and further wherein at least one of the

residues is a cyclically-constrained β-amino acid residue and at least one other of the residues is a cyclically-constrained γ-amino acid residue.

14. An isolated, unnatural polypeptide comprising six or more residues, wherein each residue is independently selected from the group consisting of α-amino acid residues, β-amino acid residues, and γ-amino acid residues, and further wherein at least two of the residues are β-amino acid residues or γ-amino acid residues or one each of a β-amino acid residue and a γ-amino acid residue.